REMARKS

The Official Action dated October 23, 2006 has been carefully considered. Additionally, the telephone interview of January 17, 2007, which Examiner Rooney and Examiner Haddad courteously afforded Applicants' representative is acknowledged and appreciated. Accordingly, the amendments presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

Although a formal agreement regarding the claims was not reached during the aforementioned interview, the claim amendment presented herein, along with the following remarks and Declaration of Dr. Lóránd Bertók, were discussed and are believed to overcome the outstanding rejections.

By the present amendment, claim 1 has been amended to delete the words "microbial and/or fungal" and add the word "bacterial". Support for this amendment may be found in the specification, for example, at page 4, line 16 and page 5, lines 4-8. It is believed that this amendment does not involve any introduction of new matter, or raise any new issue subsequent to final rejection, whereby entry is believed to be in order and is respectfully requested.

Claims 1-5, 10, 13 and 17-19 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner asserted that the claims have no written support in the specification for the broad genus "LPS derived from microbial and/or fungal endotoxin," but only have support for "LPS derived from *E. coli* bacteria". Applicants traverse this rejection. However, to expedite prosecution of this application, claim 1 has been amended to delete the words "microbial and/or fungal" and add the word "bacterial", in accordance with the teachings of the specification at page 4, line 16 and page 5, lines 4-8. In addition, Applicants submit that *E. coli* bacteria is a representative species of the genus of LPS derived from bacterial endotoxins. Specifically, to support these assertions, Applicants refer to the teachings of Trent, "Biosynthesis, transport, and modification of lipid A", *Biochem Cell Biol.* 2004 Feb;82(1):71-86, which discloses that gram-negative bacteria in general have very similar LPS structural properties. A copy of the Trent reference was previously submitted with the Amendment filed with the U.S. Patent and Trademark Office on July 24, 2006. Accordingly, it is therefore submitted that the evidence previously presented demonstrates that the specification's disclosure of LPS derived from *E. coli* bacteria provides sufficient support

for the genus of LPS derived from bacterial endotoxin. Reconsideration is respectfully requested.

Claims 1-5, 10, 13 and 17-19 were rejected under 35 U.S.C. §103(a) as being obvious and therefore unpatentable over Tulic et al, *Am. J. Resp. Cell Mol. Biol.*, Vol. 22, pp. 604-612, 2000 in view of Matricardi et al, "Microbial Products in Allergy Prevention and Therapy", *Allergy*, 2003:58:pp. 461-471, Bertók, "Stimulation of Nonspecific Resistance By Radiation-Detoxified Endotoxin", *Beneficial Effects of Endotoxins*, Plenum Publishing Corp., 1983, pp. 213-226 and Liu et al, *Current Reviews of Allergy and Clinical Immunology*, Vol. 109, pp. 379-392, 2002. The Examiner asserted that Tulic et al teach the prevention of allergy in young adult 8-10 week old rats administered LPS in aerosol; however, the Examiner asserted that Tulic et al fail to teach the administration of irradiated LPS to neonatal mammals. The Examiner asserted that Matricardi et al teach that the administration of native LPS is beneficial to treat allergy, however, a less toxic derivative of native LPS would be preferred for treatment purposes due to the severe endotoxic effects of native LPS. The Examiner asserted that Bertók teaches the use of detoxified LPS to induce tolerance to toxic effects and to mobilize the host defenses in an immunologically nonspecific fashion, but fails to teach the type of immune response stimulated by the irradiated LPS. The Examiner asserted that Liu et al teach that there is ample data demonstrating that exposure to endotoxins, such as LPS, in early life, less than two years, has been demonstrated to decrease allergic sensitization; and that frequent benign exposures to endotoxin early in life should be expected to influence immune development to prevent atopy, allergic disease and asthma. Accordingly, the Examiner asserted that one of ordinary skill in the art would have been motivated to treat the young adult 8-10 week old rats of Tulic et al with the irradiated LPS molecules of Bertók because the irradiated LPS molecules are immunostimulatory, less toxic derivatives of LPS, Matricardi et al having taught that a less toxic derivative of LPS is preferred for the treatment of allergy. The Examiner further asserted that one of ordinary skill in the art would have been motivated to treat young humans with the teachings of Matricardi et al, Tulic et al and Bertók, since Liu et al recognize that early benign exposure to native LPS can be effective in preventing allergy.

However, as will be set forth in detail below, Applicants submit that the processes defined by claims 1-5, 10, 13 and 17-19 are nonobvious over and patentably distinguishable from Tulic et al in view of Matricardi et al, Liu et al and Bertók. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

Particularly, claim 1 recites a process for inhibiting development of allergic disease. The process comprises exposing a neonatal or immature mammal or bird to irradiation-detoxified lipopolysaccharide derived from bacterial endotoxin.

Applicants submit that the combination of references does not teach, suggest or recognize the use of irradiated-LPS in a neonatal or immature mammal or bird for inhibiting the development of allergic disease. Tulic et al teach the prevention of allergy in young adult (8-10 week old) rats administered native LPS in aerosol. In contrast, the present claims are directed to processes for inhibiting development of allergic disease comprising exposing a neonatal or immature mammal or bird to irradiation-detoxified lipopolysaccharide. As noted by the Examiner, Tulic et al fail to teach, suggest or recognize the administration of irradiated LPS. In addition, Tulic et al also fail to teach, suggest or recognize the administration of irradiated LPS to a neonatal or immature mammal or bird. The specification of the present invention at page 2, lines 23-25 defines "immature" as a mammal or bird which has not completed life cycle development to its adult stage. The 8-10 week old rats in Tulic et al are not considered immature as defined by the present application because they have completed life cycle development to their adult stage as rats can reach breeding maturity, i.e., adult stage, at 6 weeks of age. See *<<health.ratzrus.co.uk/breeding.htm>>*. Accordingly, Tulic et al teach the administration of native LPS to adult rats. Therefore, Applicants submit that Tulic et al do not teach, suggest or recognize processes for inhibiting the development of allergic disease comprising exposing a neonatal or immature mammal or bird to irradiation-detoxified lipopolysaccharide as required by the present claims.

The deficiencies of Tulic et al are not overcome by the teachings of Matricardi et al. As with Tulic et al, Matricardi et al fail to teach the administration of irradiation-detoxified LPS to a neonatal or immature mammal or bird. Matricardi et al merely hypothesize that the administration of native LPS would stimulate an immune response to treat allergy in human (adult) volunteers. However, Matricardi et al note at pages 467-468 that native LPS exerts severe endotoxic effects which limit its potential use as a therapeutic agent. Accordingly, Matricardi et al conclude that the use of native LPS derivatives, such as Monophosphoryl Lipid A (MPL), are of interest over native LPS because these derivatives have similar potent adjuvant properties of native LPS, but are less toxic. The disclosures of Matricardi et al appear to teach away from the claimed invention in teaching that native LPS is limited in its potential use as a therapeutic agent to treat allergy because of its severe endotoxic effects. It is error to find obviousness when a

reference diverges from and teaches away from the invention at hand, *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). Therefore, Applicants submit that Matricardi et al also do not teach, suggest or recognize processes for inhibiting the development of allergic disease comprising exposing a neonatal or immature mammal or bird to irradiation-detoxified lipopolysaccharide as required by the present claims, and do not resolve the deficiencies of Tulic et al.

The deficiencies of Tulic et al and Matricardi et al are not overcome by the teachings of Liu et al. Liu et al disclose a review of recent studies on endotoxin exposure. However, Liu et al fail to teach, suggest or recognize the use of irradiation detoxified LPS to inhibit the development of allergic disease in a neonatal or an immature mammal or bird. Liu et al on page 385 disclose "challenge studies with different samples of cotton dust demonstrated that the endotoxin content of the cotton dust, and not the dust exposure itself, correlated with induced airflow obstruction. Since then, endotoxin exposure has been associated with respiratory symptoms and disease in a long list of workplace settings (eg, livestock handling, lab animal handling, grain and vegetable agriculture, sawmills, waste management, fiberglass manufacturing, and sick building syndrome)". Accordingly, while Liu et al recognize that endotoxins can have both beneficial and detrimental effects regarding prevention or development of allergies and asthma, Liu et al do not teach, suggest or recognize that modification of endotoxin through irradiation, or any other chemical modifications for that matter, might yield a more beneficial and less detrimental product.

The deficiencies of Tulic et al, Matricardi et al and Liu et al are not overcome by the teachings of Bertók. Bertók discloses the use of detoxified LPS to induce a nonspecific resistance in the pretreatment of various shocks, radiation diseases and infections. However, Bertók fails to teach, suggest or recognize that irradiated-LPS may be used to induce a specific resistance to inhibit the development of allergic disease in a neonatal or immature mammal or bird by stimulating an immune response. Therefore, one of ordinary skill in the art would not be motivated to look at the teachings of Bertók to inhibit the development of allergic disease in a neonatal immature mammal or bird.

More specifically, the Bertók reference discloses radiation-detoxified endotoxins, i.e., LPS, may be used to stimulate a nonspecific resistance for the pretreatment in various shocks, radiation disease and infections. A nonspecific resistance is a defense mechanism that provides a systemic response to a variety of pathogens, i.e., shocks, radiation disease and infections, without

distinguishing one pathogen from another. This general response prevents the pathogen(s) from either entering the body or inhibits the spread of the pathogen(s) after entering the body.

In contrast, the administration of irradiation-detoxified LPS to a neonatal or immature mammal or bird, as defined by the present invention, induces a specific resistance to thereby inhibit the development of an allergic disease. A specific resistance does not provide a non-distinguishing systemic response to a pathogen but, in contrast, stimulates the immune system to respond to the specific pathogen. As disclosed at page 4, line 15 - page 5, line 8 of the present specification, the administration of irradiation-detoxified LPS induces a specific resistance stimulating the Th-1 arm of the immune system to inhibit the development of an allergic disease in a neonatal or immature mammal or bird. In fact, as disclosed on page 4, lines 1-14 of the present specification, the inventors show that irradiated LPS stimulates an attenuated release of IL-1 from human peripheral blood cells. IL-1 beta is a multifunctional cytokine produced mainly by monocytes, monocyte-derived dendritic cells and macrophages. The effects of IL-1 beta for example, include: stimulation of the production and release of Th-1 type proinflammatory cytokines from Th-1 type lymphocytes: IL-2, IL-12, IL-18, TNF alpha, IFN gamma, etc.; the activation of granulocytes, the induction of fever, etc, to help the proinflammatory processes and antimicrobial defense during microbial infections. It is one of the most significant roles of native endotoxins, such as non-irradiated LPS, that protect an organism from allergic sensitization by the permanent activation of monocytes forcing them toward permanent IL-1 beta production and Th-1 stimulation.

In contrast to the Th-1 arm immune response, the Th-2 arm of immunoregulation is dominating in allergy with high levels of circulating IL-4 and IL-13. IL-13 is known to downregulate IL-1 beta gene expression of the Th-1 immune system. Therefore, the inventors have determined that by exposing a neonatal or immature mammal or bird to irradiated LPS, a potent but attenuated IL-1 beta production can be induced via the Th-1 immune response while eliminating the potentially negative side effects of native LPS.

The Examiner asserted in the Office Action, that while the Bertók reference is silent to the type of immune response stimulated by the irradiated LPS, it would now be considered a Th-1 immune response based on the cytokine profile noted in Table 1. However, Applicants submit that Table 1 of the Bertók reference merely discloses that the endotoxin tolerance-inducing, the shock-preventing, the radioprotective, the NSR-enhancing, and the immunoadjuvant capacity of

LPS was preserved after the native LPS was irradiated. Accordingly, these disclosures of Bertók only teach that irradiated LPS maintain some of its beneficial properties after it has been irradiated.

To further evidence that one skilled in the art would not be motivated to look at the teachings of the Bertók reference to inhibit the development of allergic disease in a neonatal or immature mammal or bird, Applicants direct the Examiner's attention to the Declaration of Dr. Lóránd Bertók submitted herewith. The executed Declaration will be submitted once it is received by the undersigned. Dr. Bertók serves as Professor of the Department of Microbiology at the Semmelweis Medical University in Budapest, Hungary and offers his opinions regarding the state of the art and particularly what the cited references in the Office Action teach and suggest to those skilled in the art. Opinion testimony is entitled to consideration and weight as long as the opinion is not on the ultimate legal conclusion at issue, MPEP §716, and opinion testimony regarding what the prior art taught may be entitled to considerable deference, *In re Carroll*, 202 U.S.P.Q. 571 (CCPA 1979).

According to paragraph 3 of Dr. Bertók's Declaration, he declares, based on his experience in the medical and research fields, and particularly the field of immunology, it is his opinion that there is no teaching, suggestion or reference in the cited Bertók reference to use irradiation detoxified LPS to inhibit the development of allergic disease in a neonatal or immature mammal or bird. Specifically, based on his extensive experience in the field of immunology, it is his opinion the use of irradiation detoxified LPS to induce a nonspecific resistance for the pretreatment of various shocks, radiation disease and infections does not teach, suggest or recognize the use of irradiation detoxified LPS to stimulate a specific response to inhibit the development of allergic disease in a neonatal or immature mammal or bird. Moreover, it is his opinion that there would be no motivation to look to the teachings of the Bertók reference to inhibit the development of allergic disease in a neonatal or immature mammal or bird because the Bertók reference is directed to the stimulation of a nonspecific resistance, which the claimed processes of the present invention induce a specific resistance to stimulate a Th-1 immune response to inhibit the development of allergic disease in a neonatal or immature mammal or bird as required by the claims of the present invention. One of ordinary skill in the art would, in his opinion, have no expectation that a pathogen providing the nonspecific resistance taught by the Bertók reference would be suitable for providing a different, specific resistance to inhibit the development of allergic disease in a neonatal or immature

mammal or bird. Accordingly, based on his experience, it is his opinion that there would be no teaching, suggestion or motivation to combine the Bertók reference with the other cited references because the Bertók reference specifically teaches the use of irradiation detoxified endotoxin to induce an elevated nonspecific resistance for the pretreatment of various shocks, radiation disease and infections.

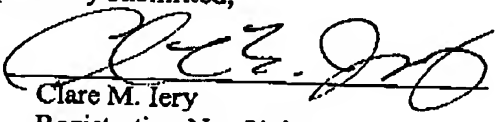
Therefore, Applicants submit that the claimed processes of inhibiting the development of allergic disease by exposing a neonatal or immature mammal or bird to a radiation detoxified lipopolysaccharide derived from microbial endotoxin, which induces a specific resistance stimulating the Th-1 immune response, are not obvious to one of ordinary skill in the art over the cited combination of references.

The Federal Circuit has held that "[w]hen a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references." *In re Rouffet*, 149 F.3d 1350, 13556 (Fed. Cir. 1998) (citing *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987)). "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984). The Examiner must give some reason as to why one of ordinary skill in the art would have been prompted to combine the teachings of the cited references to arrive at the claimed invention since it is the burden of the Examiner to establish a *prima facie* case of obviousness. The Examiner cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention; the Examiner has the burden to show some teaching or suggestion in the references to support their use in the particular claimed combination, *Smith-Kline Diagnostics, Inc. v. Helena Laboratories Corp.*, 8 U.S.P.Q. 2d 1468, 1475 (Fed. Cir. 1988). Finally, both a suggestion to combine the references and a reasonable expectation of success must be found in the art itself for a proper prima facie case of obviousness, *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988). Because the use of irradiation-detoxified LPS in the disclosures of the Bertók reference stimulate a nonspecific response for the pretreatment of various shocks, radiation disease and infections, one skilled in the art would not be motivated to look to the disclosures of the Bertók reference to induce a specific resistance to inhibit the development of allergic disease in a neonatal of immature mammal or bird.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979). As noted above, Applicants find no teaching, suggestion or reference in Tulic et al in view of Matricardi et al, Liu et al and Bertók of processes for inhibiting development of allergic disease comprising exposing a neonatal or immature mammal or bird to irradiation-detoxified lipopolysaccharide derived from bacterial endotoxin as recited by the present claims. In addition, Applicants find no teaching, suggestion or reference in Tulic et al in view of Matricardi et al, Liu et al and Bertók for modifying the disclosures therein to arrive at the claimed invention. In view of the failure of Tulic et al in view of Matricardi et al, Liu et al and Bertók to teach, suggest or recognize processes for inhibiting the development of allergic disease by exposing a neonatal or immature mammal or bird to irradiation detoxified lipopolysaccharide derived from bacterial endotoxin as recited by the claims, the references do not support a rejection of claims 1-5, 10, 13 and 17-19 under 35 U.S.C. §103. It is therefore submitted that the claimed processes as defined by claims 1-5, 10, 13 and 17-19 are nonobvious over and patentably distinguishable from the teachings of Tulic et al in view of Matricardi et al, Liu et al and Bertók, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejection of the claims under 35 U.S.C. §§103 and 112, first paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are respectfully requested.

Respectfully submitted,

By: 

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